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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,124	03/15/2001	Robert Jason Potter	0942.5030001/RWE	4601

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EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1637	23

DATE MAILED: 08/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,124	POTTER ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-21 and 63-120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-21 and 63-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to an amendment filed on April 3, 2003. Claims 11-22 and 63-120 were previously pending. Applicants amended claims 63 and 111.

2. Applicants' amendments overcame the following rejections: rejection of claims 11-22, 63-70 and 111-115 under 35 U.S.C. 112, second paragraph, and rejection of claims 63 and 21 under 35 U.S.C. 102(a) over Halvas et al.

3. Claims 11-22 and 63-120 are pending and will be examined.

Information Disclosure Statement

4. The information disclosure statement filed on April 10, 2003 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because reference AR is a copy of English language translation of a Japanese patent, therefore it does not contain a place and date of publication. This reference has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Response to Arguments

5. Applicant's arguments filed April 3, 2003 have been fully considered but they are not persuasive.

a) Regarding the rejection of claims 11-22 and 63-120 under 35 U.S.C. 112, first paragraph, written description, Applicants argue the following:

1) "The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention." (page 4, second paragraph), and "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of the filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." (page 4, third paragraph).

2) The specification provides a number of examples of mutant reverse transcriptases in Table 1 on page 29 (page 5, second paragraph).

3) The specification identifies relevant structural features, which correlate with functional characteristics and provides guidelines as to what types of mutations can be introduced in each of the structural regions to impart physical and functional characteristics (page 5, the last paragraph, continued on page 6).

b) Regarding the rejection of claims 11-22 and 63-120 under 35 U.S.C. 112, first paragraph, enablement, Applicants argue the following:

1) "..the specification clearly sets forth which mutations in specific regions of M-MLV RT and other viral RTs may be made to achieve the claimed invention" (page 7, the last paragraph).

2) The specification discloses several modes of generating reverse transcriptases with increased fidelity (page 8, the last line of the first paragraph).

With respect to a), as pointed by Applicants, the assessment has to be made comparing scope of the claims with the scope of the description. The scope of the claims is drawn to M-MLV RT sequences, each of which has 684 amino acids, and possible 20 amino acids at each position, which results in 684^{20} possible molecules. Applicants described ten such molecules ([00140]-

[00142], [00149]), which is hardly a representative number of species from the whole genus. Even assuming that only regions presumed to be in contact with the template, namely amino acids 1-279 (page 19 of the specification, [0058]) are considered, the total number of possible molecules is still very large, namely, 279^{20}, and ten molecules is not a representative number of species in this case, either. The lack of description of 279 amino acids out of 684 could hardly be considered as an omission of a nuance of the claimed invention.

With respect to b), even though the specification describes a structural general region (finger plus palm) of the M-MLV RT in which the mutations may be made in order to increase fidelity, this region consists of 279 amino acids. Applicants did not provide any other guidance as to how to determine which of these residues, when mutated, might increase fidelity. The main consideration here is the fact that mutation results cannot be predicted *a priori*, even if structure details are known, as pointed out in the previous office action. For example, mutations in residues critical to the proper folding of protein structure will result in an inactive enzyme. Therefore, the skilled artisan needs to perform undue experimentation with every mutation made in the 279 amino acid segment, since a lot of these proteins will fail to express or fold correctly. For example, as pointed out in Georgiadis et al. (Structure, Vol. 3, pp. 879-892, 1995; cited in the IDS), Val223 is a critical residue in terms of a proper fold of the protein, and is very sensitive to changes in other parts of the enzyme (page 885, the last paragraph, continued on page 886). Mutations in this residue result in decreased fidelity, as determined by Halvas et al., cited in the previous office action.

To illustrate the point further, Pfeiffer et al. (J. Virol., vol. 74, pp. 9629-9636, October 2000), in a reference published after the priority date of the instant application, teach mutation of finger and palm residues, based on the structure of M-MLV RT of Georgiadis et al. Of the 14 residues mutated, several resulted in non-viable viruses (K103A, R110A, R110K, D114H, D114N,

R116L, a combined mutation D124A + H126A), etc.) (Fig. 2). What this Figure shows is that even conservative substitutions, like R110K, result in lack of RT activity, and combinations of mutations which by themselves did not affect polymerase processivity may result in a virus with very slow replication time, e.g., D124A + H126A).

In summary, since effects of any single mutation or combination of mutations on the structure and function of the M-MLV RT cannot be predicted, Applicants' disclosure is not enabling for all mutated M-MLV reverse transcriptases, as claimed.

The rejections of claims 11-22 and 63-120 under 35 U.S.C. 112, first paragraph, written description and enablement, are maintained.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11-22 and 63-120 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants describe mutational studies of Superscript II, a mutant of the Moloney Murine Leukemia Virus reverse transcriptase (M-MLV RT), which had the following mutations in the RNAse H domain: Asp544->Gly, Asp583->Asn, Glu562->Gln (page 50, [0136], page 52, [0139]). Applicants provided information that the RNAse H domain mutations were introduced into a clone pRT601, which was described in the following patents: 5,244,797; 5,405,776; 5,668,005 and 6,063,608. As described in the '797 patent, column 12, lines 53-64, the pRT601 clone contained an

RT gene in which the amino-terminal part was from an M-MLV RT, and the carboxy terminus was "similar to the viral enzyme". Therefore, the starting material for the mutational analysis of the M-MLV RT wasn't even an M-MLV RT enzyme, but a synthetic construct. In addition, Applicants did not provide any evidence that the point mutations introduced into the pRT601 vector did indeed reduce the RNAse H activity of the reverse transcriptase. Furthermore, it is unclear whether the Superscript II enzyme had all three of the point mutations, or whether there were different versions of the Superscript II with one point mutation in each of them or with pairwise combinations of such mutations.

To summarize this part, Applicants were not is possession of an M-MLV RT enzyme as a starting material for further mutational studies, and point mutations introduced into the RNAse H domain of a 684 amino acid reverse transcriptase encoded by the pRT601 vector (further referred to as pRT601 RT) were not proven to possess reduced RNAse H activity. It is also not clear what was the starting material for further mutational analysis.

Applicants then proceeded to introduce mutations into the Superscript II enzyme. The following facts are presented in the specification: 1) mutations Y64W, R116M, K152R, Q190F, T197A and V223H resulted in RTs with increased fidelity and lower degree of nucleotide misincorporation (Table 2, [0140], [0141]); 2) mutations F309N, T197E and Y133A resulted in RTs with decreased TdT activity ([0142], [0149]), 3) mutant RTs with H204R+Y306K, H204R+Y306K +F309N mutations had increased fidelity ([0142]), and 4) mutations F309N and F309N/V223H had increased fidelity as well. The specification does not provide reasoning why these residues were chosen for making changes and how the choice of replacement amino acid was decided.

The Applicants have not described any other mutations of Y64, R116, K152, Q190, T197 and V223 that result in increased fidelity. In addition, even though possible mutations of residues

D124, H126 and Y133 are mentioned, no specific mutations were presented in the specification or shown to increase fidelity of the resulting enzyme. In terms of H204R, Y306K, and F309N mutations, only two of their possible combinations, H204R+Y306K, H204R+Y306K +F309N, were shown to impart increased fidelity on the enzyme, but no evidence was provided that any of those mutations alone or in any other combination resulted in increased fidelity.

Therefore, claims 63, 71, 91 and 107 encompass a genus of all possible M-MLV RTs, including allelic variants such as insertions, deletions and mutations, and no specific amino acid sequences of any such protein or nucleic acids encoding them, including the starting material, has been presented in the specification. Thus, the definition of an M-MLV reverse transcriptase lacks any specific structure, with the protein defined solely by its function. While some mutations are defined, such as the ones cited above, the rest of the surrounding sequence of 683 amino acids is not defined. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

8. Claims 11-22 and 63-120 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants describe mutational studies of Superscript II, a mutant of the Moloney Murine Leukemia Virus reverse transcriptase (M-MLV RT), which had the following mutations in the RNAse H domain: Asp544->Gly, Asp583->Asn, Glu562->Gln (page 50, [0136], page 52, [0139]). Applicants provided information that the RNAse H domain mutations were introduced into a clone pRT601, which was described in the following patents: 5,244,797; 5,405,776; 5,668,005 and 6,063,608. As described in the '797 patent, column 12, lines 53-64, the pRT601 clone contained an

RT gene in which the amino-terminal part was from an M-MLV RT, and the carboxy terminus was "similar to the viral enzyme". Therefore, the starting material for the mutational analysis of the M-MLV RT wasn't even an M-MLV RT enzyme, but a synthetic construct. In addition, Applicants did not provide any evidence that the point mutations introduced into the pRT601 vector did indeed reduce the RNAse H activity of the reverse transcriptase. Furthermore, it is unclear whether the Superscript II enzyme had all three of the point mutations, or whether there were different versions of the Superscript II with one point mutation in each of them or with pairwise combinations of such mutations. Therefore, it is not clear what was the starting material for further mutational analysis.

Applicants then proceeded to introduce mutations into the Superscript II enzyme. The following facts are presented in the specification: 1) mutations Y64W, R116M, K152R, Q190F, T197A and V223H resulted in RTs with increased fidelity and lower degree of nucleotide misincorporation (Table 2, [0140], [0141]); 2) mutations F309N, T197E and Y133A resulted in RTs with decreased TdT activity ([0142], [0149]), 3) mutant RTs with H204R+Y306K, H204R+Y306K +F309N mutations had increased fidelity ([0142]), and 4) mutations F309N and F309N/V223H had increased fidelity as well. The specification does not provide reasoning why these residues were chosen for making changes and how the choice of replacement amino acid was decided.

The Applicants have not described any other mutations of Y64, R116, K152, Q190, T197 and V223 that result in increased fidelity. In addition, even though possible mutations of residues D124, H126 and Y133 are mentioned, no specific mutations were presented in the specification or shown to increase fidelity of the resulting enzyme. In terms of H204R, Y306K, and F309N mutations, only two of their possible combinations, H204R+Y306K, H204R+Y306K +F309N, were shown to impart increased fidelity on the enzyme, but no evidence was provided that any of those mutations alone or in any other combination resulted in increased fidelity.

Therefore, claims 63, 71, 91 and 107 encompass a genus of all possible M-MLV RTs, including allelic variants such as insertions, deletions and mutations, and no specific amino acid sequences of any such protein or nucleic acids encoding them, including the starting material, has been presented in the specification. The skilled artisan would therefore have to perform experiments on all possible variants of the M-MLV RT to determine which of these enzymes, when mutations suggested by the specification were introduced into them, had the property of increased fidelity and reduced RNAse H activity. In addition, the definition of "increased fidelity" provided in the specification on pages 19 and 20, paragraph [0060], reads "preferably about 1.5 to about 10,000 fold", but no standard for comparison is provided. In the paragraph one of possible comparison methods given is reference RT being a wild-type protein vs. mutated one, but no definition is given of what the "wild-type" means. For example, in the present case, would it be the pRT601 RT or the Superscript II RT (and which Superscript II?). No definition is provided regarding "reduced or substantially reduced RNAse H activity".

Due to the large quantity of experimentation necessary to determine all possible mutations in all possible M-MLV reverse transciptases which will result in increased enzyme fidelity, the lack of direction and guidance presented in the specification regarding creation of all possible mutations in all possible M-MLV reverse transciptases which will result in increased enzyme fidelity, the absence of working examples directed to making such mutations in M-MLV reverse transcriptases, the unpredictability of the effects of mutations on protein structure and function (see references below), undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

In M-MLV RT, Val223 is a part of the conserved YXDD motif in reverse transcriptases and has been implicated in the fidelity of DNA synthesis. The conserved Tyr222 was mutated to Phe,

Ser and Ala, but only Y-> F mutant had increased fidelity, whereas the Y-> S and Y-> A mutants had significantly reduced activity (Kaushik et al., Biochemistry, vol. 38, pp. 2617-2627, 1999; cited in the IDS). Glutamine 190 mutations to Asn and Ala had significantly reduced polymerase and pyrophosphorylase activities (Jin et al., J. Biol. Chem., vol. 274, pp. 20861-20868, 1999; cited in the IDS). Arg 110 replacements with Lys, Ala or Glu resulted in a loss of polymerase activity and no impairment of RNAse H function (Chowdhury et al., Biochemistry, vol. 35, pp. 16610-16620, 1996; cited in the IDS). Halvas et al. (J. Virology, vol. 74, pp. 312-319, January 2000) describe an assay for determining fidelity of reverse transcriptases and testing the V223M, V223S, V223A, V223I and Y598V mutants of M-MLV RT using the assay. The V223M, V223S, V223A mutants had higher error rates than the non-mutated RT, and the V223I mutant had the same error rate.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 71, 82, 91 and 102 are rejected under 35 U.S.C. 102(a) as being anticipated by Halvas et al. (J. Virology, vol. 74, pp. 312-319, January 2000; cited in the previous Office action).

Halvas et al. teach M-MLV reverse transcriptase which has been mutated to at a position of Valine 223, which resides in the primer-template recognition region. The mutations were Val223Met, Val223Ser and Val223Ala (abstract; Table 2; page 317).

11. No references were found teaching or suggesting claims 11-22, 63-70, 72-81, 83-90, 92-101 and 103-120, but they are rejected for reasons given above.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS TS
July 31, 2003

BJ FORMAN, PH.D.
PRIMARY EXAMINER